Phase II trial of APR-246 in combination with azacitidine as maintenance therapy for *TP53* mutated AML or MDS following allogeneic stem cell transplant

Protocol No.:	A19-11172
IND No.:	139738
Principal Investigator:	Asmita Mishra, MD [redacted]
Sponsor:	Aprea Therapeutics AB [redacted]
Medical Monitor:	[redacted]
Protocol Version:	3.0
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CONFIDENTIAL

INVESTIGATOR'S STATEMENT

1. I have carefully read this protocol entitled "Phase II trial of APR-246 in combination with azacitidine as maintenance therapy for *TP53* mutated AML or MDS following allogeneic stem cell transplant" and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.

2. I understand that this study will not be initiated without approval of the appropriate Institutional Review Committee/Independent Ethics Committee (IRB/IEC), and that all administrative requirements of the governing body of the Institution will be complied with fully.

3. Informed written consent will be obtained from all participating patients in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013).

4. I will enroll patients who meet the protocol criteria for entry.

5. I understand that my signature on each completed Case Report Form (CRF) indicates that I have carefully reviewed the complete set of CRFs and accept full responsibility for the contents thereof.

6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor unless this requirement is superseded by the Food and Drug Administration, a Competent Authority of the European Union or another Regulatory Authority.

Investigator:

Name: _____ Telephone: _____

Address: _____

Signature: _____ Date: _____

Sponsor Representative:

Signature: _____ Date: _____

[redacted]

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CLINICAL STUDY SYNOPSIS

Name of Sponsor: Aprea Therapeutics AB	**Name of Monitor:** [redacted]

Title of the Study:
Phase II trial of APR-246 in combination with azacitidine as maintenance therapy for *TP53* mutated AML or MDS following allogeneic stem cell transplant

Protocol Number: A19-11172

Principal Investigator:
Asmita Mishra (Moffitt Cancer Center, Tampa FL)

Study Drugs: APR-246 and azacitidine

Clinical Phase: II

Objectives:

Primary Objectives:

1. To assess relapse-free survival (RFS) in patients with *TP53* mutated AML or MDS who receive combination maintenance treatment with APR-246 with azacitidine after undergoing allogeneic hematopoietic stem cell transplant (HSCT).
2. To evaluate the safety and tolerability of APR-246 in combination with azacitidine as maintenance treatment post-HSCT.

Secondary Objectives:

1. To assess the overall survival (OS).
2. To assess non-relapse mortality (NRM).
3. To assess time to progression (TTP).
4. To evaluate cumulative incidence of Grades II-IV and III-IV acute graft versus host disease (GVHD).
5. To evaluate 12-month cumulative incidence of mild, moderate, and severe GVHD.
6. To describe event-free survival (EFS)

Exploratory Objectives:

1. To examine the effect of pre- and post-transplant minimal residual disease (MRD) (*TP53* variant allele frequency, VAF) on RFS and overall survival (OS).

2. To determine if p53 protein expression and other potential genomic biomarkers at baseline before and after HSCT predicts potential effect on RFS and OS.
3. To determine if *TP53* clonal suppression (serial VAF in bone marrow) after HSCT correlates with outcomes.
4. To evaluate APR-246 plasma pharmacokinetics (PK) when administered with azacitidine after transplantation.
5. To evaluate post-transplant donor engraftment via chimerism studies in blood and bone marrow.

Endpoints:

Primary Endpoints:

1. RFS
2. Incidence, severity, relatedness of adverse events (AEs) and/or laboratory abnormalities

Secondary Endpoints:

1. OS
2. NRM
3. Time to progression or relapse
4. Incidence and grade of acute and chronic GVHD (cumulative)
5. Incidence and grade of acute and chronic GVHD (1-year)
6. EFS

Exploratory Endpoints:

1. MRD defined by *TP53* VAF
2. RFS and OS in relation to baseline p53 protein expression (IHC) and other potential genomic biomarkers
3. RFS and OS in relation to clonal suppression, i.e., depth and duration of *TP53* VAF reduction in bone marrow samples repeated every 3 months
4. PK parameters: C_{max}, $AUC_{0\text{-}inf}$, $T_{1/2}$
5. Post-transplant donor engraftment via chimerism studies in blood and bone marrow (whole marrow and CD3/CD33 fractions)

Study Design:

This is a multi-center, open label, Phase II clinical trial to assess the safety and efficacy of APR-246 in combination with azacitidine as maintenance therapy after allogeneic HSCT for patients with *TP53* mutant AML or MDS.

To be eligible to participate in this study, all patients must have either: 1) pre-screening next generation sequencing (NGS) on peripheral blood (PB) or bone marrow (BM) samples at time of HSCT work up to determine presence of *TP53* mutation status or, 2) previously documented evidence of *TP53* mutation by NGS on PB or BM samples.

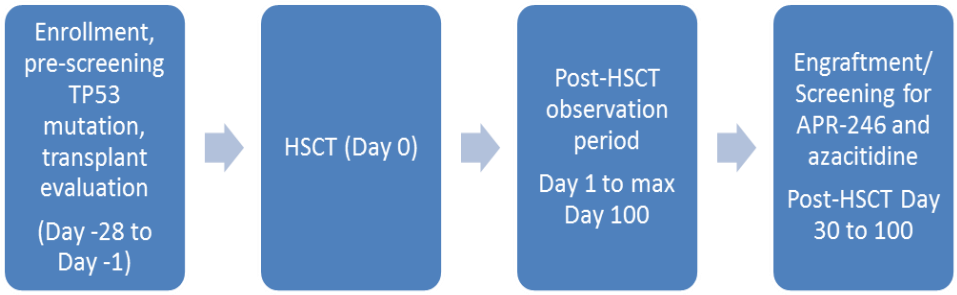
Patients will sign consent and be prescreened for *TP53* mutant AML or MDS before they have a HSCT (Day 0). During the post-HSCT period (Day 1 to 100 post-HSCT), patients are screened for eligibility to receive APR-246 and azacitidine maintenance treatment. In order to proceed with APR-246 and azacitidine treatment, neutrophil and platelet engraftment (recovery) must be confirmed between Day 30 to Day 100 post-HSCT. APR-246 and azacitidine must be initiated no more than 28 days after confirmation.

APR-246 will be administered on Days 1-4, with azacitidine on Days 1-5, of every 28-day cycle. Patients may receive a maximum of 12 cycles of treatment. Patients may continue to receive study treatment in the setting of relapse or progression, up to a maximum of 12 cycles, provided they are continuing to derive benefit in the opinion of the Investigator.

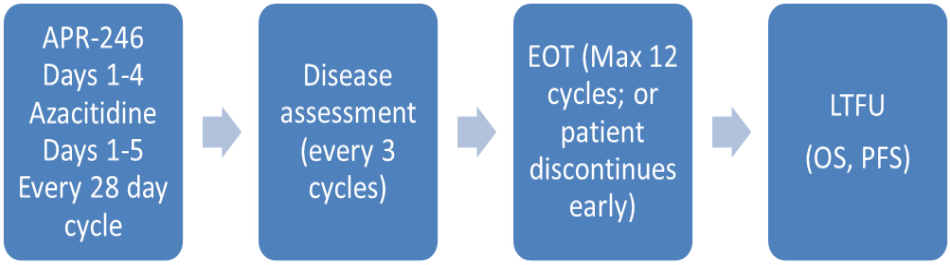
A safety evaluation will be performed by the Safety Monitoring Committee after the first 6 patients have completed 1 cycle of APR-246 and azacitidine combination therapy. The Committee will decide if it is appropriate to continue at the current dose; or, in the event the combination is not tolerated the dose of APR-246 will be reduced for subsequent patients.

Trial Overview:

Prescreening (prior to APR-246 and azacitidine)



APR-246 and Azacitidine Treatment Period, EOT and LTFU



Dose Modification:

	APR-246	Azacitidine
Starting dose level	3.7g 4h infusion days 1-4 q28d cycle	36 mg/m^2 sc or iv, days 1-5 q28d cycle
-1 dose level reduction	3.3g 4h infusion days 1-4 q28d cycle	36 mg/m^2 sc or iv, days 1-5 q28d cycle
-2 dose level reduction	3.0g 4h infusion days 1-4 q28d cycle	36 mg/m^2 sc or iv, days 1-5 q28d cycle

Number of patients: At least 31 patients

Inclusion Criteria:

Pre-Screening:

These observations will be done ≤ 28 days prior to beginning conditioning chemotherapy in anticipation for allograft infusion.

1. Documentation of a *TP53* gene mutation (which is not benign or likely benign) by NGS based on local evaluation with study eligibility confirmed centrally.
2. Must provide a pre-HSCT bone marrow biopsy.
3. Age ≥18 years at the time of signing the informed consent form
4. Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act Authorization (HIPAA) for US sites) obtained from the participant or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
5. Patient has confirmed, morphologically documented MDS or AML by WHO criteria.
6. Patient is considered a suitable candidate for HSCT and has an acceptable source of allogeneic donor hematopoietic stem cells, as defined per

institutional practice (allogeneic HSCT for any donor source [matched sibling, unrelated donor (URD), mismatched URD, related haploidentical,] and any graft source [BM, PB], and any non-study conditioning [myeloablative conditioning (MAC), reduced intensity conditioning (RIC), or non-myeloablative conditioning (NMA)] will be permitted). Additionally, any standard (non-study) GVHD prophylaxis regimen will be permitted.

7. Females must either:
    a. Be of non-childbearing potential
        i. postmenopausal (defined as at least 1 year without menses) prior to screening, or
        ii. documented as surgically sterilized at least 1 month prior to the screening visit
    b. Or, if of childbearing potential,
        i. Agree not to try to become pregnant during the study and for 6 months after the final study drug administration
        ii. And have a negative serum pregnancy test at screening
        iii. And, if heterosexually active, agree to consistently use highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and throughout the study period and for 6 months after final study drug administration.
8. Females must agree not to breastfeed or donate ova throughout the study drug treatment period and for 6 months after the final study drug administration.
9. Males (even if surgically sterilized), and their partners who are women of childbearing potential must be using highly effective contraception in addition to a barrier method throughout the study drug treatment period and for 127 days after the final study drug administration.
10. Males must not donate sperm throughout the study drug treatment period and for 127 days after the final study drug administration.

Exclusion Criteria Pre-Transplant:

1. Patient has had a prior allogeneic transplant.
2. Patient has any of the following cardiac abnormalities (as determined by treating physician):
    a. Myocardial infarct within six months prior to registration
    b. New York Heart Association Class III or IV heart failure or known left ventricular ejection fraction (LVEF) < 40%
    c. A history of familial long QT syndrome

d. Symptomatic atrial or ventricular arrhythmias not controlled by medications
e. QTc ≥ 470 ms calculated from a mean of 3 ECG readings using Fridericia's correction ($QTcF = QT/RR^{0.33}$). Patients with QTc ≥ 470 ms and bundle branch block and/or pacemaker rhythm may be enrolled following approval by the Medical Monitor.

Post-transplant Inclusion Criteria for APR-246 and azacitidine treatment:

1. Patient has received one allogeneic transplant for AML or MDS. At time of treatment, patient must in morphologic remission for AML or MDS as defined as < 5% blasts for AML and ≤ 5% blasts for MDS, and in cytogenetic remission with no morphologic characteristics of acute leukemia (e.g., Auer Rods) in the BM with no evidence of extramedullary disease such as central nervous system involvement or granulocytic sarcoma. Patients with CR with incomplete count recovery (CRp or CRi) are allowed. Incomplete platelet recovery (CRp) is defined as CR with platelet count < 100 x 10^9/L. Incomplete blood count recovery (CRi) is defined as CR with neutropenia < 1 x 10^9/L with or without complete platelet recovery. Red blood cell count (RBC) and platelet transfusion independence is not required.
2. Any standard (non-study) conditioning [MAC, RIC, or NMA] will be permitted. Acceptable source of allogeneic donor hematopoietic stem cells, as defined per institutional practice (allogeneic HCT for any donor source [matched sibling, URD, mismatched URD, or related haploidentical] and any PB or BM graft source.
3. Patient is ≥ 30 days and ≤ 100 days from hematopoietic cell infusion.
4. Patient is in complete remission after the transplant and has achieved engraftment. Engraftment is defined as ANC≥500/μL and platelets ≥ 20000/μL on 3 consecutive measurements (each occurring at least 1 day apart). The patient must not have had a platelet transfusion within 7 days prior to the first measurement.
5. Patients who have developed grades II-IV acute GVHD will be allowed to initiate maintenance therapy based on the following criteria:
   - Does not require high dose steroids as defined as dosage of > 0.5 mg/kg of prednisone (or equivalent) daily dose within 1 week of post-HSCT screening
   - No escalation of systemic immunosuppression in terms of increase of corticosteroids or addition of new agent/modality within 2 weeks of post-HSCT screening. Dose adjustments (both increase and decrease) of GVHD preventative medications such as calcineurin inhibitors or sirolimus to achieve therapeutic trough levels, is allowed. Topical skin and topical gastrointestinal steroids are allowed.

6. Females must either:
   - Be of non-childbearing potential
     - postmenopausal (defined as at least 1 year without menses) prior to screening, or
     - documented as surgically sterilized (e.g., hysterectomy or tubal ligation) at least 1 month prior to the screening visit
   - Or, if of childbearing potential,
     - Agree not to try to become pregnant during the study and for 6 months after the final study drug administration
     - And have a negative serum pregnancy test at screening
     - And, if heterosexually active, agree to consistently use highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and throughout the study period and for 6 months after final study drug administration.
7. Females must agree not to breastfeed or donate ova throughout the study drug treatment period and for 6 months after the final study drug administration.
8. Males (even if surgically sterilized), and their partners who are women of childbearing potential must be using highly effective contraception in addition to a barrier method throughout the study drug treatment period.
9. Males must not donate sperm throughout the study drug treatment period.
10. Agrees not to participate in another interventional study while on treatment.
11. Karnofsky Performance Status 70 or greater is required.
12. Patient has adequate organ function as defined by the following laboratory values:
    a. Creatinine clearance > 30 mL/min by Cockcroft-Gault formula;
    b. Total serum bilirubin < 1.5 x ULN unless due to Gilbert's Syndrome, underlying disease of MDS, hemolysis or considered an effect of regular blood transfusions;
    c. ALT/AST < 2.5 x ULN, unless due to underlying disease of MDS.

Post-transplant Exclusion Criteria for APR-246 and azacitidine treatment:

1. Use of umbilical cord blood donor and stem cell source.
2. Patient has uncontrolled infection. Definitive therapy for infection is required and must have no signs of progression within 7 days of first day of study drug treatment.
3. Use of investigational agent within 14 days of pre-HSCT screening or

anytime thereafter.

4. Use of hypomethylating agent, cytotoxic chemotherapeutic agents, or experimental agents (agents that are not commercially available) for the treatment of MDS or AML within 14 days of the first day of pre-HSCT screening or anytime thereafter.
5. Patient has used experimental therapy for acute GVHD at any time post-transplant. If unsure of the definition of "experimental", discussion with the Medical Monitor is recommended.
6. Patient requires treatment with supplemental oxygen not including usage of non-invasive CPAP at night.
7. Patient has any of the following cardiac abnormalities (as determined by treating physician):
   a. Myocardial infarct within six months prior to registration
   b. New York Heart Association Class III or IV heart failure or known LVEF<40%
   c. A history of familial long QT syndrome
   d. Symptomatic atrial or ventricular arrhythmias not controlled by medications
   e. QTc ≥ 470 ms calculated from a mean of 3 ECG readings using Fridericia's correction ($QTcF = QT/RR^{0.33}$). Patients with QTc ≥ 470 ms and bundle branch block and/or pacemaker rhythm may be enrolled after approval by the Medical Monitor.

Duration of treatment:

APR-246 and azacitidine maintenance therapy will continue for a maximum of 12 cycles or until one of the following criteria applies:

- Evidence of disease relapse defined as ≥5% blasts for AML patients or >5% blasts for MDS patients. Patients who are continuing to derive clinical benefit in the opinion of the investigator may remain on study treatment following relapse.
- Inter-current illness that prevents further administration of treatment.
- Unacceptable adverse event (AE)(s).
- Patient decides to withdraw from treatment.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Patient begins other treatment for underlying disease (i.e., MDS or AML).
- Grade 3-4 acute GVHD or Severe chronic GVHD.

If the patient discontinues treatment early, then the reason for treatment discontinuation and the date the patient was removed will be documented. Patients removed from treatment for unacceptable AEs will be followed until resolution or stabilization of the AE.

Patients may continue to receive study treatment in the setting of relapse or progression, up to a maximum of 12 cycles, provided they are continuing to derive benefit in the opinion of the Investigator.

Criteria for evaluation:

Efficacy: Bone marrow aspirate and biopsy following cycle 3, cycle 6, cycle 9, and cycle 12, or when clinically indicated, and monthly CBC.

Safety: CTCAE v5.0. Weekly history and physical for AE assessment (CTCAE v5.0), including CBC with diff, CMP and LDH for the first month on treatment, then monthly.

GVHD assessment (Harris, 2016; Jagasia, 2015) will be performed weekly for the first month on treatment, then monthly.

PK: Cycle 1 only. Pre-dose, 45 min (+/- 5min) after SOI, at EOI (4 hr +/- 30 min after SOI), 5-6 hr after SOI, 24 hr after SOI/Day 2 (before Day 2 dose).

Statistical Methods:

Demographic and clinical variables for the study patients will be summarized using descriptive statistics (mean, standard deviation, median, inter-quartile range, range, frequency counts and percentages). Safety and efficacy data will be analyzed overall as well as separately for each dose cohort when appropriate.

Analysis Populations:

Safety Evaluable Population:

All subjects who are registered on the study and received any dose of APR-246 or azacitidine.

Efficacy Evaluable Population:

All subjects who are registered on the study and received at least one dose of APR-246 or azacitidine, and have at least one efficacy assessment, or had

relapse/progression.

Sample Size:
The primary endpoint of the study is the relapse-free survival (RFS) at 12 months. The primary analysis will be done using Kaplan-Meier methodology. Based upon the published data, the risk of relapse and non-relapse mortality in *TP53* mutated MDS is assumed to be ~40% and ~30% at 1 year, respectively. Thus, the assumptions used for the sample size determination are:

- the null hypothesis: the RFS at 1 year is 30%,
- the alternative hypothesis: the RFS at 1 year is 50% or higher,
- accrual time: 24 months,
- follow-up time: 12 months,
- the RFS follows the exponential distribution.

With a one-sided significance level of 10%, 31 subjects will provide 90.1% power to test the null hypothesis against the alternative. The expected number of events during the study is 23 and the power was computed by a one-sided one-sample logrank test. The final analysis will be conducted when the follow-up time for all censored patients exceed 12 months. The null hypothesis will be rejected if a one-sided p-value by the log-rank test is less than or equal to 0.1.

Efficacy Analyses:
All efficacy analyses will be provided by using Efficacy Evaluable population.

Relapse-Free Survival
The primary endpoint, RFS, is defined as the time from the date of registration to disease relapse after SCT, or death, whichever occurs earlier. If patients discontinued treatment due to toxicity, and withdrew consent without relapse disease (RD) or death at the time of data cut off, RFS will be censored at the date of the last assessment.

RFS will be analyzed using Kaplan-Meier methodology. Kaplan-Meier curves will be plotted. Median relapse-free survival will be estimated and their 95% confidence intervals based on Brookmeyer-Crowley methodology will be calculated.

Event-Free Survival (EFS)
EFS is defined as from registration to the first of: morphologic disease relapse, death from any cause, reappearance of a pre-transplant cytogenetic alteration, donor lymphocyte infusion (DLI) for the purpose of treating MDS/AML, or

institution of anti-MDS/AML therapy.

Overall Survival
Overall survival (OS) is defined as the number of days from the date of registration to the date of death, irrespective of the cause. In the event of no death, overall survival will be censored at the last known alive date.

OS will be analyzed using the similar methods as RFS.

Non-Relapse Mortality (NRM)
NRM is defined as time to deaths without relapse/recurrence. Deaths from any cause without prior progression are events. Events related to the disease such as relapse and progression are competing events. Patients lost to follow-up are censored.

NRM will be analyzed using the similar methods as RFS.

Time to Progression (TTP)
Time to progression or relapse is time to first event related to the disease, such as disease progression, disease relapse/recurrence, death from disease progression, and/or initiation of any therapy given to prevent relapse. Deaths without prior relapse/recurrence (i.e., NRM) are competing events.

TTP will be analyzed using the similar methods as RFS.

Safety Analyses:
Safety data including adverse events, vital signs, laboratory data, ECG, physical exam will be tabulated for the Safety Evaluable population. Adverse events will be tabulated by body system, preferred term, severity, and relationship. The tabulation of laboratory parameters will include the normal ranges for each parameter. Each value will be classified as falling above, below, or within the normal range. Laboratory parameters will also be tabulated by maximum NCI-CTCAE v5 severity grade. Incidence and grade of acute and chronic GVHD at 1-year and cumulative will be summarized by number (%) of subjects for each dose level and overall.

LIST OF ABBREVIATIONS

AE	adverse events

ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
$AUC_{0\text{-}inf}$	area under curve, time 0 to infinity
BM	bone marrow
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CBC	complete blood count
CIBMTR	Center for International Blood and Marrow Transplant Research Repository
CMP	complete metabolic panel
CNS	central nervous system
CPAP	continuous positive airways pressure
CR	complete remission
CRi	complete remission with incomplete blood recovery
CRp	complete remission with incomplete platelet recovery
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLI	donor lymphocyte infusions
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EFS	event-free survival
ECOG	Eastern Cooperative Oncology Group (performance status)
EOI	end of infusion
EOT	end of treatment
ESA	erythropoiesis-stimulating agents
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GVHD	graft versus host disease
HCT	hematopoietic cell transplant
HIPAA	Health Insurance Portability and Accountability Act Authorization
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IHC	immunohistochemistry
IMP	investigational medicinal product
iv	intravenous
IPSS	International Prognosis Scoring System
IRB/IEC	Institutional Review Board/Independent Ethics Committee
LDH	lactate dehydrogenase
LLN	lower limit normal
LTFU	long term follow-up
LVEF	left ventricular ejection fraction
MAC	myeloablative conditioning
MDS	myelodysplastic syndromes
MRD	minimal residual disease

ms	millisecond
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next generation sequencing
NMA	non-myeloablative conditioning
NMT	no more than
NRM	non-relapse mortality
OS	overall survival
PB	peripheral blood
PK	pharmacokinetics
PLD	pegylated liposomal doxorubicin
PRBC	packed red blood cells
QTc and QTcF	corrected QT interval, by Fredericia
RBC	red blood cells
RD	relapse disease
RFS	relapse-free survival
RIC	reduced intensity conditioning
RP2D	recommended phase II dose
sc	subcutaneous
SOI	start of infusion
$T_{1/2}$	half-life
TBL	total bilirubin
TTP	time to progression
ULN	upper limit normal
URD	unrelated donor
VAF	variant allele frequency
WHO	World Health Organization

1.0 GENERAL INFORMATION

1.1 Protocol Number and Title of the Study

A19-11172: Phase II trial of APR-246 in combination with azacitidine as maintenance therapy for *TP53* mutated AML or MDS following allogeneic stem cell transplant

1.2 Sponsor

Aprea Therapeutics AB
Nobels väg 3
SE-171 65 Solna
Sweden

1.3 Monitor

[redacted]

1.4 Signature Authorization

The protocol will be signed by Aprea Therapeutics.

1.5 Principal Investigator

[redacted]

2.0 BACKGROUND INFORMATION

2.1 Introduction

Transplantation of healthy hematopoietic stem cells from an allogeneic donor (HSCT) is the only curable treatment option to improve outcomes for otherwise incurable myeloid diseases such as acute myeloid leukemias (AML) and myelodysplastic syndromes (MDS). With the development of safer transplant conditioning regimens and supportive care measures, transplant can now be offered as a potential curative option to a wider population. However, the potential benefits can be offset by potential resurgence of the disease after HSCT. Disease recurrence is a major cause of treatment failure in patients with AML or MDS who undergo allogeneic HSCT to treat high risk disease, with limited treatment options in the post-HSCT relapsed setting. Thus maintenance strategies need to be explored after transplantation to prevent disease recurrence and improve upon survival.

2.2 *TP53* Mutations in MDS and AML

Next generation sequencing (NGS) is becoming more commonly employed as a means to provide detailed and rapid assessment of genome studies that continues to enhance the diagnostic, prognostic, and therapeutic capabilities within myeloid malignancies.[1] Most commonly utilized NGS myeloid panels incorporate 20-50 genes and can identify mutations in the vast majority of patients,[2,3] several of which that have been independently associated with decreased survival.[4] More recent investigations have uncovered the most negative prognostic factor in MDS patients noting the impact of the mutation status of *TP53*. Not only are (non-benign) *TP53* mutations associated with decreased OS in mutated patients,[4] but also predicts poor response and resistance in patients treated with the only currently available FDA-approved disease modifying agents in MDS, lenalidomide and azacitidine (AZA).[4,5,6,7,8] Similarly, patients with AML with evidence of *TP53* mutation are associated with NCCN poor risk AML, complex karyotype, and monosomal karyotype and demonstrate poor overall survival and relapse-free survival similar to what has been reported in MDS.[9,10]

2.3 *TP53* Mutations in HCT

Genetic profiling of patients at time of undergoing HSCT continues to inform clinicians regarding risk stratification of allogeneic transplant recipients. Mutations of *TP53* strongly predict for lack of benefit to HCT, and additionally demonstrate the prognostic significance of *TP53* mutation as patients with complex karyotype without

mutant *TP53* had similar survival to patients with normal karyotype.[11,12] Using the Center for International Blood and Marrow Transplant Research Repository (CIBMTR), Lindsley and colleagues furthermore reported the largest data analysis to date on the prognostic impact genomic mutations in HSCT recipients for MDS. At least 1 genomic abnormality was detected in nearly 80% of patients who underwent HSCT. *TP53* mutations were represented in 19% of all patients and at a higher frequency (34%) in patients with Intermediate-2 or High Risk stratification by the International Prognosis Scoring System (IPSS). In multivariate analysis, *TP53* was independently associated with shorter survival and shorter time to relapse in comparison to no evidence of *TP53* mutation. Three-year overall survival for *TP53* mutated patients was 20% with median overall survival of approximately 8 months, in comparison to those that did not have *TP53* mutation having a median OS of approximately 2 years.[12] This study underscores the importance of alternative strategies for *TP53* mutated patients particularly those eligible curable intent therapy utilizing HSCT.

2.4 Azacitidine After Allogeneic HCT

Azacitidine (AZA) is a DNA methyltransferase inhibitor that shows significant clinical activity in both MDS and AML.[13,14] Additionally, AZA has been shown to an effective salvage therapy in patients who relapse after HCT.[15] Given the efficacy of AZA in these settings, maintenance strategies have been evaluated post-allogeneic transplant to prevent disease recurrence. The efficacy of low-dose AZA after allogeneic transplantation was originally reported in AML [16] and subsequently in a larger phase I dose finding study including AML and MDS patients.[17] In a cohort of forty-five patients who receive 4 cycles of post-HCT AZA, one year event-free survival and overall survival were reported as 58% and 77%, respectively, with reversible thrombocytopenia noted to be the dose-limiting toxicity. Tolerability and efficacy of AZA for one year after HCT has been reported by Craddox et al.[18] Thirty seven patients were treated in AZA in the peri-transplant period with the day 100 and 1 year NRM was 0% and 8%, respectively, with no patients having any evidence of chronic graft versus host disease, underscoring the tolerability of the treatment. The 1-year and 2-year RFS were 57% and 49%, respectively, with patients demonstrating CD8+ T cell response demonstrating reduced relapse rate. Thus AZA dosing of 36 mg/m^2 subcutaneously for five consecutive days is effective and tolerable, and will be utilized at this dose for this study.

2.5 APR-246

[redacted]

2.6 Rationale for Current Study

[redacted]

[redacted]

2.7 Number of Patients

Approximately 31 patients.

2.8 Potential Risks

[redacted]

[redacted]

2.9 Characteristics of a Well-Conducted Trial

The following characteristics of an adequate and well-conducted trial will be implemented:

1. The Investigators will be well qualified by scientific training and experience.

2. Detailed Case Report Forms (CRFs) will be completed for every patient.

3. Requirements for institutional ethics review as set forth by the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC), Title 21 Code of Federal Regulations (CFR) Part 56, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Sections 3 and 4, and the terms of the Declaration of Helsinki (2013), will be followed.

4. Requirements for informed consent in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013), will be followed.

5. Safety data will be recorded and evaluated.

6. Routine monitoring visits will be conducted by the Sponsor's representative ([redacted]) to ensure data accuracy.

7. Drug accountability will be strictly maintained.

8. This trial will be conducted according to Good Clinical Practice (GCP), the protocol and applicable regulatory requirements.

3.0 TRIAL OBJECTIVES AND PURPOSE

3.1 Primary Objectives

1. To assess relapse-free survival (RFS) in patients with *TP53* mutated AML or MDS who receive combination maintenance treatment with APR-246 with azacitidine after undergoing allogeneic hematopoietic stem cell transplant (HSCT).
2. To evaluate the safety and tolerability of APR-246 in combination with azacitidine as maintenance treatment post-HSCT.

3.2 Secondary Objectives

1. To assess the overall survival (OS).
2. To assess non-relapse mortality (NRM).
3. To assess time to progression (TTP).
4. To evaluate cumulative incidence of Grades II-IV and III-IV acute graft versus host disease (GVHD).
5. To evaluate 12-month cumulative incidence of mild, moderate, and severe GVHD.
6. To describe event-free survival (EFS).

3.3 Exploratory Objectives

1. To examine the effect of pre- and post-transplant MRD (*TP53* variant allele frequency, VAF) on RFS and OS.
2. To determine if p53 protein expression and other potential genomic biomarkers at baseline before and after HSCT predicts potential effect on RFS and OS.
3. To determine if *TP53* clonal suppression (serial VAF in bone marrow) after HSCT correlates with outcomes.
4. To evaluate APR-246 plasma pharmacokinetics (PK) when administered with azacitidine after transplantation.
5. To evaluate post-transplant donor engraftment via chimerism studies in blood and bone marrow.

3.4 Endpoints

3.4.1 Primary Endpoints

1. RFS
2. Incidence, severity, relatedness of adverse events (AEs) and/or laboratory abnormalities

3.4.2 Secondary Endpoints

1. OS
2. NRM
3. Time to progression or relapse
4. Incidence and grade of acute and chronic GVHD (cumulative)
5. Incidence and grade of acute and chronic GVHD (1-year)
6. EFS

3.4.3 Exploratory Endpoints

1. MRD defined by *TP53* VAF
2. RFS and OS in relation to baseline p53 protein expression (IHC) and other potential genomic biomarkers
3. RFS and OS in relation to clonal suppression, i.e., depth and duration of *TP53* VAF reduction in BM samples repeated every 3 months
4. PK parameters: C_{max}, $AUC_{0\text{-}inf}$, $T_{1/2}$
5. Post-transplant donor engraftment via chimerism studies in blood and bone marrow (whole marrow and CD3/CD33 fractions)

4.0 TRIAL DESIGN

4.1 Overview of Trial Design

This is a multi-center, open label, Phase II clinical trial to assess the safety and efficacy of APR-246 in combination with azacitidine as maintenance therapy after allogeneic HSCT for patients with *TP53* mutant AML or MDS.

To be eligible to participate in this study, all patients must have either: 1) pre-screening NGS on peripheral blood (PB) or bone marrow (BM) samples at time of HSCT work up to determine presence of *TP53* mutation status or, 2) previously documented evidence of *TP53* mutation by NGS on PB or BM samples.

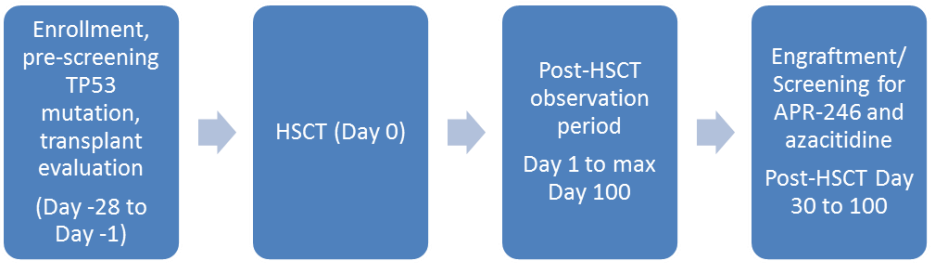
Patients will sign consent and be prescreened for *TP53* mutant AML or MDS before they have a HSCT (Day 0). During the post-HSCT period (Day 1 to 100 post-HSCT), patients are screened for eligibility to receive APR-246 and azacitidine maintenance treatment. In order to proceed with APR-246 and azacitidine treatment, neutrophil and platelet engraftment (recovery) must be confirmed between Day 30 to Day 100 post-HSCT. APR-246 and azacitidine must be initiated no more than 28 days after confirmation.

APR-246 will be administered on Days 1-4, with azacitidine on Days 1-5, of every 28 day cycle. Patients may receive a maximum of 12 cycles of treatment. Patients may continue to receive study treatment in the setting of relapse or progression, up to a maximum of 12 cycles, provided they are continuing to derive benefit in the opinion of the Investigator.

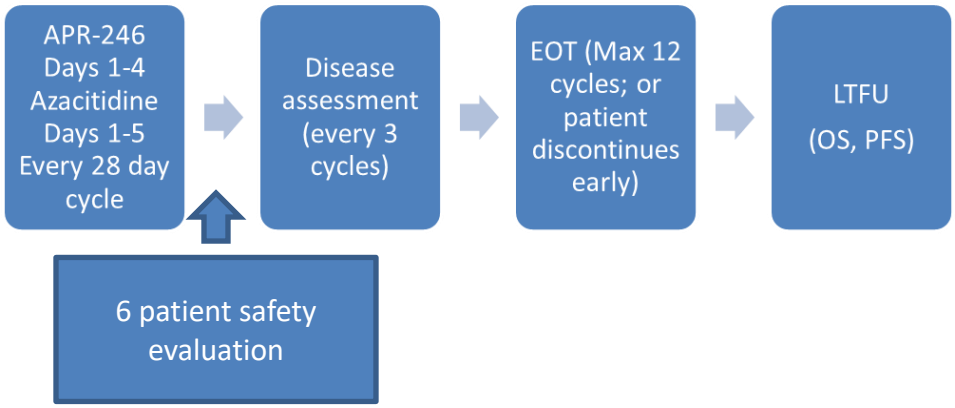
A safety evaluation will be performed by the Safety Monitoring Committee after the first 6 patients have completed 1 cycle of APR-246 and azacitidine combination therapy. The Committee will decide if it is appropriate to continue at the current dose; or, in the event the combination is not tolerated (e.g. patients experience dose limiting toxicity) the dose of APR-246 will be reduced for subsequent patients.

Figure 1: Trial Overview

Enrollment, Pre-screening, Pre-/Post-HSCT APR-246 Screening



APR-246 and Azacitidine Treatment Period, EOT and LTFU



4.2 Safety Evaluation-First 6 Patients

A safety evaluation will be performed by the Safety Monitoring Committee after the first 6 patients have completed 1 cycle of APR-246 and azacitidine combination therapy. If >1 of 6 patients experience any of the following toxicities, then the APR-246 dose will be reduced for subsequently enrolled patients.

- Treatment related non-hematological CTCAE grade 3-4 toxicity that lead to dose modification or withdrawal.
- Absolute neutrophil count (ANC) not recovering to >500/µL by day 56 of a cycle in the absence of active leukemia/myelodysplasia.
- Grade 3 metabolic/electrolyte abnormalities that are clinically significant, and not adequately controlled within 72 hours.

- Grade 3 nausea/vomiting/diarrhea or CNS toxicity that does not resolve within 28 days despite treatment interruption and maximum medical therapy.

4.3 Study Stopping Criteria

If any of the following occur, the study will be temporarily paused until a full review by the safety monitoring committee is completed:

- Any death (other than death related to progressive disease) that occurs within 30 days of study drug administration.

4.4 End of Study

The end of the study is defined as the date of the last visit of the last patient undergoing the trial.

4.5 Duration of Therapy

Maintenance therapy will continue for a maximum of 12 cycles (28 days/cycle) from first dose of APR-246, or until one of the following criteria applies:

- Evidence of disease relapse defined as ≥5% blasts for AML patients or >5% blasts for MDS patients. Patients who are continuing to derive clinical benefit in the opinion of the investigator may remain on study treatment following relapse.
- Inter-current illness that prevents further administration of treatment.
- Unacceptable AEs.
- Participant decides to withdraw from treatment.
- General or specific changes in the patient's condition render the patient. unacceptable for further treatment in the judgment of the investigator.
- Participant begins other treatment for underlying disease (MDS or AML).
- Grade 3-4 acute GVHD or Severe chronic GVHD.

If the participant discontinues treatment early, then the reason for treatment discontinuation and the date the participant was removed will be documented. Participants removed from treatment for unacceptable AEs will be followed until resolution or stabilization of the AE. Participants that discontinue treatment early will continue to be followed for relapse, if not yet documented, and survival.

Patients may continue to receive study treatment in the setting of relapse or progression, up to a maximum of 12 cycles, provided they are continuing to derive benefit in the opinion of the Investigator.

4.6 Trial Discontinuation

For reasonable cause, either the Investigator or the Sponsor may terminate this study prematurely. Written notification of the termination is required. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements (non-compliance).
- Lack of evaluable and/or complete data.
- Decision to modify the developmental plan of the drug.
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

4.7 Drug Accountability/Disposition of Clinical Trial Supplies

Drug accountability records will be maintained for all clinical trial supplies.

All unused clinical trial supplies will be returned to the Sponsor, or at the Sponsor's directive, destroyed by the site following site standard practices for disposal.

4.8 Registration

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-study evaluations. Patients must meet all eligibility requirements listed in Section 5.0. Patients will be registered on the study by using the [redacted] Interactive Web Response System (IWRS) automated patient registration system (see the Study Operations Manual for specific instructions).

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

To participate in this study, patients must meet:

- Transplant and enrollment criteria in Sections 5.1.1-5.1.2; and,
- APR-246 and azacitidine treatment criteria in Sections 5.2.1-5.2.2.

5.1 Pre-Screening

5.1.1 Inclusion Criteria

These observations will be done ≤ 28 days prior to beginning conditioning chemotherapy in anticipation for allograft infusion.

1. Documentation of a *TP53* gene mutation (which is not benign or likely benign) by NGS based on local evaluation with study eligibility confirmed centrally.
2. Must provide a pre-HSCT bone marrow biopsy.
3. Age ≥18 years at the time of signing the informed consent form
4. Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act Authorization (HIPAA) for US sites) obtained from the participant or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
5. Patient has confirmed, morphologically documented MDS or AML by WHO criteria.
6. Patient is considered a suitable candidate for HSCT and has an acceptable source of allogeneic donor hematopoietic stem cells, as defined per institutional practice (allogeneic HSCT for any donor source [matched sibling, unrelated donor (URD), mismatched URD, related haploidentical] and any graft source [BM, PB], and any non-study conditioning [myeloablative conditioning (MAC), reduced intensity conditioning (RIC), or non-myeloablative conditioning (NMA)] will be permitted). Additionally, any standard (non-study) GVHD prophylaxis regimen will be permitted.
7. Females must either:
    a. Be of non-childbearing potential
        i. postmenopausal (defined as at least 1 year without menses) prior to screening, or
        ii. documented as surgically sterilized at least 1 month prior to the screening visit

b. Or, if of childbearing potential,
    i. Agree not to try to become pregnant during the study and for 6 months after the final study drug administration
    ii. And have a negative serum pregnancy test at screening
    iii. And, if heterosexually active, agree to consistently use highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and throughout the study period and for 6 months after final study drug administration.

8. Females must agree not to breastfeed or donate ova throughout the study drug treatment period and for 6 months after the final study drug administration.
9. Males (even if surgically sterilized), and their partners who are women of childbearing potential must be using highly effective contraception in addition to a barrier method throughout the study drug treatment period and for 127 days after the final study drug administration.
10. Males must not donate sperm throughout the study drug treatment period and for 127 days after the final study drug administration.

5.1.2 Exclusion Criteria

1. Patient has had a prior allogeneic transplant.
2. Patient has any of the following cardiac abnormalities (as determined by treating physician):
    a. Myocardial infarct within six months prior to registration
    b. New York Heart Association Class III or IV heart failure or known left ventricular ejection fraction (LVEF) < 40%
    c. A history of familial long QT syndrome
    d. Symptomatic atrial or ventricular arrhythmias not controlled by medications
    e. QTc ≥ 470 ms calculated from a mean of 3 ECG readings using Fridericia's correction ($QTcF = QT/RR^{0.33}$). Patients with QTc ≥ 470 ms and bundle branch block and/or pacemaker rhythm may be enrolled after approval by Medical Monitor.

5.2 Post-transplant Criteria for APR-246 and Azacitidine Treatment

5.2.1 Inclusion Criteria

1. Patient has received one allogeneic transplant for AML or MDS. At time of

treatment, patient must in morphologic remission for AML or MDS as defined as < 5% blasts for AML and ≤ 5% blasts for MDS, and in cytogenetic remission with no morphologic characteristics of acute leukemia (e.g., Auer Rods) in the BM with no evidence of extramedullary disease such as central nervous system involvement or granulocytic sarcoma. Patients with CR with incomplete count recovery (CRp or CRi) are allowed. Incomplete platelet recovery (CRp) is defined as CR with platelet count < 100 x 10^9/L. Incomplete blood count recovery (CRi) is defined as CR with neutropenia < 1 x 10^9/L with or without complete platelet recovery. Red blood cell count (RBC) and platelet transfusion independence is not required.

2. Any standard (non-study) conditioning [MAC, RIC, or NMA] will be permitted. Acceptable source of allogeneic donor hematopoietic stem cells, as defined per institutional practice (allogeneic HCT for any donor source [matched sibling, URD, mismatched URD, related haploidentical] and any graft source [BM, PB].
3. Patient is ≥ 30 days and ≤ 100 days from hematopoietic cell infusion.
4. Patient is in complete remission after the transplant and has achieved engraftment. Engraftment is defined as ANC≥500/μL and platelets ≥ 20000/μL on 3 consecutive measurements (each occurring at least 1 day apart). The patient must not have had a platelet transfusion within 7 days prior to the first measurement.
5. Patients who have developed grades II-IV acute GVHD will be allowed to initiate maintenance therapy based on the following criteria:
   - Does not require high dose steroids as defined as dosage of > 0.5 mg/kg of prednisone (or equivalent) daily dose within 1 week of post-HSCT screening
   - No escalation of systemic immunosuppression in terms of increase of corticosteroids or addition of new agent/modality within 2 weeks of post-HSCT screening. Dose adjustments (both increase and decrease) of GVHD preventative medications such as calcineurin inhibitors or sirolimus to achieve therapeutic trough levels, is allowed. Topical skin and topical gastrointestinal steroids are allowed.
6. Females must either:
   - Be of non-childbearing potential
     - postmenopausal (defined as at least 1 year without menses) prior to screening, or
     - documented as surgically sterilized (e.g., hysterectomy or tubal ligation) at least 1 month prior to the screening visit
   - Or, if of childbearing potential,
     - Agree not to try to become pregnant during the study and for 6 months after the final study drug administration

- And have a negative serum pregnancy test at screening
- And, if heterosexually active, agree to consistently use highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and throughout the study period and for 6 months after final study drug administration.

7. Females must agree not to breastfeed or donate ova throughout the study drug treatment period and for 6 months after the final study drug administration.
8. Males (even if surgically sterilized), and their partners who are women of childbearing potential must be using highly effective contraception in addition to a barrier method throughout the study drug treatment period.
9. Males must not donate sperm throughout the study drug treatment period.
10. Agrees not to participate in another interventional study while on treatment.
11. Karnofsky Performance Status 70 or greater is required. (APPENDIX A)
12. Patient has adequate organ function as defined by the following laboratory values:
    a. Creatinine clearance > 30 mL/min by Cockcroft-Gault formula;
    b. Total serum bilirubin < 1.5 x ULN unless due to Gilbert's Syndrome, underlying disease of MDS, hemolysis or considered an effect of regular blood transfusions;
    c. ALT/AST < 2.5 x ULN, unless due to underlying disease of MDS.

5.2.2 Exclusion Criteria

1. Use of umbilical cord blood donor and stem cell source.
2. Patient has uncontrolled infection. Definitive therapy for infection is required and must have no signs of progression within 7 days of first day of study drug treatment.
3. Use of investigational agent within 14 days of pre-HSCT screening or anytime thereafter.
4. Use of hypomethylating agent, cytotoxic chemotherapeutic agents, or experimental agents (agents that are not commercially available) for the treatment of MDS or AML within 14 days of the first day of pre-HSCT screening or anytime thereafter.
5. Patient has used experimental therapy for acute GVHD at any time post-transplant. If unsure of the definition of “experimental”, discussion with the Medical Monitor is recommended.
6. Patient requires treatment with supplemental oxygen not including usage of non-invasive CPAP at night.
7. Patient has any of the following cardiac abnormalities (as determined by

treating physician):

a. Myocardial infarct within six months prior to registration
b. New York Heart Association Class III or IV heart failure or known LVEF< 40%
c. A history of familial long QT syndrome
d. Symptomatic atrial or ventricular arrhythmias not controlled by medications
e. QTc ≥ 470 ms calculated from a mean of 3 ECG readings using Fridericia's correction ($QTcF = QT/RR^{0.33}$). Patients with QTc ≥ 470 ms and bundle branch block and/or pacemaker rhythm may be enrolled after approval by Medical Monitor.

5.3 Withdrawal Criteria

Protocol therapy will be discontinued at any time if any of the following situations occur:

1. Relapsed disease, unless Investigator believes patient is receiving clinical benefit.
2. The development of toxicity which, in the Investigator's judgment, precludes further therapy.
3. Patient refusal.
4. Lost to follow-up/noncompliance.
5. Intercurrent illness.
6. At the discretion of the Investigator.
7. Pregnancy.
8. Study termination.
9. Initiation of anti-MDS/AML therapy or DLI for purpose of treating MDS/AML.

5.3.1 Withdrawn Subjects

When a patient is removed from the study, the Investigator will clearly document the reason in the medical record and complete the appropriate case report form page describing the reason for discontinuation. In addition, every effort should be made to complete the appropriate assessments listed in Section 7.3.

5.4 Noncompliance

All instances of noncompliance and all resulting protocol deviations will be entered in the case report forms.

6.0 TREATMENT OF SUBJECTS

6.1 Drug Preparation and Administration

Patients will receive APR-246 and azacitidine on days 1-4 and 1-5, respectively, every 28-day cycle. APR-246 and azacitidine are administered in the clinic.

Figure 2: Overview of APR-246 and Azacitidine Treatment Per Cycle

APR-246 administration	↓	↓	↓	↓			Next Cycle:
Day	**1**	**2**	**3**	**4**	**5**	**6-28**	**D29 prior cycle/D1**
Azacitidine administration	↑	↑	↑	↑	↑		+4 wk window permitted

6.1.1 APR-246

At the pharmacies, the IMP vials are to be stored at 2-8ºC (35.6-46.4°F). At the pharmacies and at the study centers, the prepared APR-246 study product (diluted in sodium chloride solution) is to be stored at not more than 25ºC. The infusion should be completed within 24 hours from the time of preparation (see Study Manual).

A fixed dose of 3.7g APR-246 will be administered as an intravenous infusion daily on days 1-4 of each 28 day cycle. Total infusion time is 4 hours, administered in 2 consecutive steps:

1) 1.6 g for the first 45 minutes (+/- 2 min)
2) 2.1 g over 3 hours 15 minutes (+/- 15 min)

Detailed instructions on vial concentration, preparation and dispensing can be found in the Pharmacy Manual. The infusion timing, including start/stop times and the time of rate change, must be recorded.

6.1.2 Azacitidine

Azacitidine (36 mg/m^2) is administered sc or iv for 5 consecutive days. The same route of administration should be used each day of a cycle.

Azacitidine will be administered within 1 hour following the end of the APR-246 infusion.

6.2 Criteria for Retreatment and Dose Modifications

This section outlines the requirements for proceeding with treatment with APR-246, and the protocol rules for APR-246 dose modification due to toxicity.

ECGs
For all patients

- Patients with screening QTcF ≥470 ms (average from triplicate ECG) are excluded from the study. Rescreening is allowed.
- At a minimum, ECG should be performed pre-dose and end-of-infusion (EOI) on Day 1, Cycle 1-4. This ECG may be done as single or replicate (i.e. duplicate or triplicate, average QTcF should be used). Patients with screening or any pre-dose 450 ≤ QTc < 470 ms should be subject to more intense ECG monitoring (see below).
- If a pre-dose ECG shows QTcF ≥470 ms the QTc reading should be manually confirmed. Serum concentrations of electrolytes should be controlled and adjusted if necessary. Concomitant medication should be reviewed and adjusted if necessary. A new ECG may be done at any time, even the same day. The patient should not be treated unless QTc is <470. If the dose is given later on the same day, follow the planned cycle. If the dose cannot be given, omit that dose from the cycle.
- If the patient at any time during the study starts with a concomitant medication known to prolong the QT interval, a pre-dose and EOI ECG should be performed for the next planned dose
- If any ECG during the study shows a significant change (vs baseline or pre-dose) in QTcF, defined as either i) increase >60 ms, ii) increase >25 %, or iii) increase to an absolute value ≥500 ms, the dose should be held/interrupted. If the QTc prolongation is confirmed by a manual read, the therapy should stop until the cause has been identified and eliminated (electrolyte disturbance or concomitant drug) and QTc is again <470ms. Discontinue APR-246 permanently, if other causes for clinically significant QTcF increase are excluded.

Additional monitoring for patients with 450 ≤ QTc < 470 ms at baseline or <u>any</u> pre-dose measurement

- ECG should be performed pre-dose and end-of-infusion (EOI) for all doses (Day 1-4, all cycles). This ECG may be done as single or replicate (i.e., duplicate or triplicate, average QTcF should be used).
- Dose should be held for pre-dose QTcF ≥470 ms (see above). For a post-dose

(EOI) ECG showing >60 ms increase vs pre-dose or any QTcF >500 ms, see above.

- Patients should avoid QTc prolonging drugs on infusion days, if possible, and have any electrolyte imbalance checked and corrected (CTCAE ≤Grade 1).
- If repeated QTcF measurements show a stable QTcF <450, or if the patient is stable in the interval 450 to <470 ms with no significant change at EOI (several cycles of treatment) the investigator may discuss with the Medical Monitor to decrease the number of ECGs performed in the study.

Other toxicity

All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 5). Once a dose has been reduced during a treatment cycle, re-escalation will not be permitted during any subsequent cycle (with exception of CNS events). If the administration of APR-246 is interrupted for reasons other than toxicity, then treatment with APR-246 may be resumed at the same dose. The same provision applies if the patient experienced an unacceptable toxicity not specifically described in this section, provided that this toxicity resolved to ≤ CTCAE grade 1, unless otherwise specified.

Day 1 of next cycle treatment with APR-246 and azacitidine can be delayed for up to 4 weeks (28 days) to allow for count recovery at Investigator discretion pending discussion with the Sponsor and Medical Monitor. Non-hematologic grade 4 treatment related adverse events will lead to permanent discontinuation, irrespective of recovery time, unless otherwise specified.

Exceptions would include nausea/vomiting/diarrhea which can be controlled by medications and/or asymptomatic electrolyte imbalances which can be corrected. In addition, in most instances, patients that experience a prolonged treatment interruption because of an adverse event and/or a grade 3 adverse event will decrease the dose of study drug after their recovery (see tables in this section for dose adjustment guidelines).

If any other drug-related grade 3 or 4 toxicity that is not clearly related to azacitidine is observed, APR-246 dose must be reduced for the next and subsequent cycles.

6.2.1 Dose Modifications

Table 1: Dose Modifications for APR-246

	APR-246	Azacitidine
Starting dose level	3.7g 4h infusion days 1-4 q28d cycle	36 mg/m^2 sc or iv, days 1-5 q28d cycle
-1 dose level reduction	3.3g 4h infusion days 1-4 q28d cycle	36 mg/m^2 sc or iv, days 1-5 q28d cycle
-2 dose level reduction	3.0g 4h infusion days 1-4 q28d cycle	36 mg/m^2 sc or iv, days 1-5 q28d cycle

APR-246 is partially eliminated via the kidney and moderate renal impairment, defined by a creatinine clearance, or estimated glomerular filtration rate value of >30 to <60 mL/min, can lead to increases in plasma levels of approximately 30%. Therefore, for patients with moderate renal impairment, the dose of APR-246 should be reduced by 33% from the current dose (Table 2).

Table 2: APR-246 Dose Modification in the Setting of Moderate Renal Impairment

APR-246 Dose	**33% Reduced Dose**	**Loading Dose (over 45 min)**	**Maintenance Dose (over 3 hr and 15 min)**
3.7 g	2.5 g	1.1 g	1.4 g
3.3 g	2.2 g	1.0 g	1.2 g
3.0 g	2.0 g	0.9 g	1.1 g
<3.0 g	Please consult with Medical Monitor		

Monitoring renal function by assessment of serum creatinine prior to infusion of APR-246 is recommended in all patients.

Patients requiring >2 dose reductions for APR-246 will be permanently discontinued from study drug. Patients who permanently discontinue APR-246 or azacitidine should have follow-up within 30 days after discontinuation of all study treatment or resolution of the AE to ≤ grade 1, whichever occurs first, that includes all study assessments appropriate to monitor the event.

Azacitidine dose modifications will be per the prescribing information and institutional guidelines. Patients may continue with APR-246 without azacitidine if ≥

2 dose modifications have been due to cytopenias. APR-246 study drug may resume at last dosage received.

Any changes in dose must be recorded on the Dosage Administration Record CRF.

Table 3: APR-246-Recommended Dose Modifications and Criteria for Treatment Interruption and Re-Initiation for Hepatorenal Toxicities

Hepatorenal Toxicities	
Worst toxicity (CTCAE 5 Grade)†	**Dose Modifications for APR-246**
Serum Creatinine	
Grade 1 (< 1.5 × ULN)	Maintain dose level
Grade 2 (> 1.5 to 3.0 × ULN)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 – 6.0 × ULN)	If resolved in ≤ 7 days, then ↓ 1 dose level If resolved in > 7 days, discontinue patient from APR-246
Grade 4 (> 6.0 × ULN)	Permanently discontinue patient from APR-246
Bilirubin‡	
Grade 1 (> ULN - 1.5 × ULN)	Maintain dose level with LFTs* monitored as per protocol
Grade 2 (> 1.5 - 3.0 × ULN) with ALT or AST ≤ 3.0 × ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 × ULN) with ALT or AST ≤ 3.0 × ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days, discontinue patient from APR-246
Grade 4 (> 10.0 × ULN)	Permanently discontinue patient from APR-246
AST or ALT	
Grade 1 (> ULN - 3.0 × ULN if baseline was normal; 1.5 - 3.0 × baseline if baseline was abnormal)	Maintain dose level with LFTs* monitored per protocol
Grade 2 (> 3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal) without total bilirubin elevation to > 2.0 × ULN	Omit dose until resolved to ≤ Grade 1, then If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 5.0 - 20.0 × ULN if baseline was normal; > 5.0 – 20.0 x baseline if baseline was abnormal) without total bilirubin elevation to > 2.0 × ULN	Omit dose until resolved to ≤ Grade 1, then If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal) without bilirubin elevation to > 2.0 × ULN	Permanently discontinue patient from APR-246
*(LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 × ULN), alkaline phosphatase.	
† Common Terminology Criteria for Adverse Events (CTCAE) version 5. ‡ For patients with Gilbert's syndrome, these dose modifications apply to changes in direct bilirubin only. * LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 × ULN), alkaline phosphatase.	

Table 4: APR-246 Dose Modifications for Neutropenia with or without Fever

Parameter †	**Worst toxicity** ‡	**Dose modifications for APR-246**	
Neutropenia with or without fever	Grade 3 or 4 neutropenic fever or worsening neutropenia from baseline to Grade 4 without fever	1st occurrence	• Interrupt dosing and monitor patient; treat promptly. • Resume at current dose level if neutropenia and fever (if present) resolve to baseline within 7 days after onset. • If toxicity does not resolve to baseline despite maximal medical intervention(s) within 7 days of onset, then reduce APR-246 by 1 dose level once the toxicity resolves to baseline. • Initiate or reassess prophylaxis measures. Refer to Sections 6.3.3 and 6.3.4 for supportive management guidelines specific to infection prophylaxis and neutropenia, respectively.
		2nd occurrence	• Hold all study treatments and monitor patient; treat promptly. • Assess current infection prophylaxis and adjust treatment plan as clinically indicated. Refer to Sections 6.3.3 and 6.3.4 for supportive management guidelines specific to infection prophylaxis and neutropenia, respectively. • While APR-246 and azacitidine are interrupted, consult with study medical monitor to determine if a dose modification of APR-246 is warranted.
Thrombocytopenia	Grade 4 (platelet count <25 x 10^9/L) and major bleeding event	Permanently discontinue patient from APR-246.	

† Only applicable for patients with normal baseline absolute neutrophil count (ANC) and platelets)
‡ Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Table 5: APR-246-Recommended Dose Modifications and Criteria for Treatment Interruption and Re-Initiation for Non-Hematological Toxicities

Other Non-Hematological Toxicities	
Worst toxicity (CTCAE 5 Grade)†	**Dose Modifications for APR-246**
CNS – dizziness, dyskinesia and ataxia	
Grade 1	Maintain dose level
Grade 2	If resolved with medical therapy, continue same dose level If not resolved despite treatment interruption and maximal medical therapy, stop infusion and ↓ 1 dose level for subsequent dose
Grade 3	If resolved with medical therapy, continue same dose level If not resolved despite treatment interruption and maximal medical therapy, stop infusion and ↓ 1 dose level for subsequent dose
Grade 4	Permanently discontinue patient from APR-246.
Infusion Related Reaction	
Grade 1	Maintain dose level.
Grade 2	Maintain dose level; Symptomatic management (e.g., antihistamines, corticosteroids, narcotics, IV fluids)
Grade 3	If resolved in < 4 hours with treatment interruption and medical therapy (e.g., antihistamines, corticosteroids, narcotics, IV fluids), continue same dose level and rate. If not resolved in < 4 hours despite treatment interruption and maximal medical therapy, stop infusion and ↓ 1 dose level for subsequent dose
Grade 4	Permanently discontinue patient from APR-246.
Nausea/Vomiting/Diarrhea	
Grade 1	Maintain dose level
Grade 2	If resolved, then maintain dose level If not resolved despite maximal medical therapy, then ↓ 1 dose level
Grade 3	If resolved, then maintain dose level If not resolved despite maximal medical therapy, then ↓ 1 dose level
Grade 4	Permanently discontinue patient from APR-246
Any Other Toxicity	
Grade 3 or 4	Delay dose until resolution to ≤ Grade1, then ↓ 1 dose level
† Common Terminology Criteria for Adverse Events (CTCAE) version 5.	

6.3 Concomitant Treatment

6.3.1 GVHD During Therapy

If a participant develops new onset GVHD, or experiences an increase in the severity of pre-existing GVHD requiring an escalation of immunosuppressive medication, every effort should be made to continue the study drug without any dose reduction. If the participant is unable to take study drug as a result of GVHD, the study drug can be withheld until the participant is able to resume treatment.

6.3.1.1 Management of Acute GVHD

Acute GVHD should be managed per institutional guidelines. Therapies considered standard are allowed and use of investigational therapy while on study drug is not allowed.

6.3.1.2 Management of Chronic GVHD

Chronic GVHD should be managed per institutional guidelines. Therapies considered standard are allowed and use of investigational therapy while on treatment is not allowed.

[redacted]

[redacted]

[redacted]

As [redacted]

The following recommendations were taken from National Comprehensive Cancer Network Guidelines for Prevention and Treatment of Cancer-Related Infections (Version 1.2021).

Table 6. Recommendations for prevention and treatment of cancer-related infections

Organism	Recommendations
Bacterial	Consider fluoroquinolone or other suitable anti-bacterial prophylaxis during neutropenia

Fungal	Consider prophylaxis during neutropenia and for anticipated mucositis. Assess risk for Pneumocystis jirovecii pneumonia and select agent(s) as clinically indicated.
Viral	Start treatment with anti-viral medication in the setting of neutropenia and continually assess the risk for viral infection during treatment with anti-cancer therapy.

Refer to Section 6.2 for guidance on APR-246 dose modification in the setting severe infection and/or infestation event, using the parameter titled, "Any Other Toxicity" (Table 5).

Refer to Section 6.3 for a description of drugs that are not allowed to be used while a patient is on study treatment.

6.3.4 Management of Neutropenia with or without Fever

Monitor complete blood counts at the time of study enrollment and throughout the course of study treatment. Supportive measures such as antimicrobials for prophylaxis or in the setting of prolonged myelosuppression, and/or at the first signs of infection are recommended to reduce the risk of a serious or severe infection that may lead to a fatal outcome in the setting of neutropenia with or without fever (see Section 6.3.3).

Myeloid growth factors may be used in the setting of severe or prolonged neutropenia. Refer to Section 6.3 for a description of drugs that are not allowed to be used while a patient is on study treatment.

Refer to Section 6.2.1 for APR-246 dose modification in the setting of severe or life-threatening neutropenia with or without fever.

6.3.5 General Concomitant Medications and Supportive Care Guidelines

6.3.5.1 Antimicrobials

Antibacterial, antiviral and antifungal prophylaxis and treatment during and after allogeneic HSCT are recommended and can be administered based on local institutional guidelines.

6.3.5.2 Tapering of GVHD Prophylaxis

Tapering of immunosuppression should be followed per institutional practice in the absence of GVHD. There are no formal recommendations given that participants receiving HCT from any type of donor, after any conditioning and receiving any GVHD prophylaxis regimen are eligible.

6.3.5.3 Donor Lymphocyte Infusions

Pre-emptive/prophylactic administration of donor lymphocytes for disease progression (morphological or molecular) is not permitted in this protocol. DLI for infectious complications or modulation of T cell donor chimerism after allograft administration per institutional guidelines is allowed. For any unresolved questions regarding DLI administration should be discussed with the Medical Monitor.

6.3.6 Prohibited Therapy

- Other anticancer therapy: Anticancer therapy (chemotherapy, endocrine, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is enrolled in the treatment portion of the trial. If such agents are required for a patient then, the patient must be permanently discontinued from the treatment portion of the study. Exception: for breast cancer or prostate patients on adjuvant hormonal therapy (e.g., anastrozole/tamoxifen or leuprolide) who have been disease free for at least 1 year.

- Other investigational therapies: Other investigational therapies must not be used while the patient is on the study including those for disease or GVHD.

6.3.7 Other Concomitant Treatment (Medication and Non-medication Therapy)

In general, the use of any concomitant medications/therapies deemed necessary for the care of the patient are allowed, with specific exceptions below. Prophylactic anti-emetic therapy is permitted where indicated. Participating centers will adhere to institutional practice regarding the monitoring of serum levels of immunosuppressive agents such as tacrolimus or azoles.

Any disease progression that requires other specific anti-tumor therapy will be cause for discontinuation from the trial.

6.3.8 Permitted Medications

6.3.8.1 Growth Factors

Erythropoiesis-stimulating agents (ESAs) are not allowed for anemia during the study. G-CSF is allowed for evidence of neutropenia.

6.3.8.2 Anticoagulant Therapy

Subjects who are taking warfarin (or equivalent) may participate in this study; however, it is recommended that prothrombin time (PT-INR) and PTT be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin, low molecular weight heparin and oral anticoagulants are permitted.

6.3.8.3 Blood Products

The use of blood products to include packed red blood cells (PRBCs) and platelet transfusions are permitted and to be given at the discretion of the treating physician. Recommended guidelines for transfusion include a platelet threshold of 10,000/L for platelet transfusion and a hemoglobin threshold of 8.0g/dL for PRBC transfusion or as clinically deemed by the discretion of treating physician.

6.4 Monitoring Subject Compliance

Study drug will be administered only to eligible patients by the appropriate study personnel. Drug dispensing and administration records will be maintained.

7.0 STUDY EVALUATIONS

Unscheduled visits and laboratory monitoring may occur as needed. Window of 3 days applies except where noted.

7.1 Pre-Screening

APPENDIX B lists visits and assessments prior to starting APR-246 and azacitidine. Unscheduled visits and laboratory monitoring may occur as needed.

7.1.1 Pre-Screening (Day -28 to -1 prior to HSCT)

- Sign informed consent
- *TP53* mutation confirmation
- Disease assessment: BM aspirate and/or biopsy sample must be collected prior to the start of the pre-transplant conditioning regimen.
- Pregnancy test (women of child-bearing potential only)
- ECGs; see Table 7.

7.1.2 Day 0

- Transplant

7.1.3 Post-Transplant, APR-246 Screening Period (Day 1 to 100)

Post-HSCT evaluation will occur as per institutional standard practices.

APR-246/azacitidine screening period occurs during Day 30 to 100 post-HSCT. The date will vary but should start (Day -28 relative to first dose) as soon as engraftment and the requirements in Section 7.1.4 are confirmed. The first dose must be administered no more than 28 days after confirmation.

The procedures listed below should be performed within 28 days prior to the first dose, or as indicated. Starred (*) procedures should be done within 3 days prior to the first dose.

- Sign informed consent
- Disease assessment
- Eligibility
- Karnofsky performance status

- Medical history and Transplant Details
- Physical exam with Weight*
- Vital signs*
- CBC*
- CMP*
- ECGs*; see Table 7.
- Pregnancy test (women of child-bearing potential only)*
- Pre-treatment/baseline Bone marrow (BM)/Aspirate (BMA) for correlatives/exploratory: see Table 9
- GVHD monitoring
- Chimerism, immune reconstitution
- Monitor adverse events
- Concomitant medications

7.1.4 Confirmation to Proceed to APR-246 and Azacitidine Treatment (Day 30 to 100)

- Bone marrow exam, including cytomorphology, cytogenetic assessment, and flow cytometry analysis.
- Engraftment is defined as ANC≥500/μL and platelets ≥ 20000/μL on 3 consecutive measurements (each occurring at least 1 day apart). The patient must not have had a platelet transfusion within 7 days prior to the first measurement.
- Once this BM biopsy confirms CR and all other eligibility is confirmed, the patient must start APR-246 and azacitidine treatment within 28 days of confirmation.

7.2 APR-246 and Azacitidine Treatment

APPENDIX B lists visits and assessments. Unscheduled visits and laboratory monitoring may occur as needed. The first dose must be administered no more than 28 days after confirmation.

7.2.1 Cycle 1, Day 1

- APR-246 (administered Days 1-4)
- Azacitidine (administered Days 1-5)
- PK sampling Day 1 pre- and post-dosing: see Section 8.4
- ECGs; see Table 7.

- Adverse events
- Concomitant medications

7.2.2 Cycle 1, Days 2, 3, 4, 5

- APR-246 (administered Days 1-4)
- Azacitidine (administered Days 1-5)
- Additional ECG monitoring in select patients; see Section 6.2
- PK sampling predose Day 2: see Section 8.4
- Adverse events
- Concomitant medications

7.2.3 Cycle 1, Days 7, 14, 21

- Vital Signs
- CBC
- CMP
- Adverse events
- Concomitant medications

7.2.4 Cycle 1, Day 28

- Physical exam with Weight
- Vital signs
- CBC
- CMP
- GVHD monitoring
- Adverse events
- Concomitant medications
- Disease assessment (blood)

7.2.5 Cycles 2-4, Day 1 (Day 29 of prior cycle)

First dose of next cycle may be delayed up to 4 weeks.

- APR-246 (administered Days 1-4)
- Azacitidine (administered Days 1-5)
- Physical exam with Weight; Does not need to be repeated if done within 3 days prior
- Vital signs; Does not need to be repeated if done within 3 days prior
- CBC; Does not need to be repeated if done within 3 days prior

- CMP; Does not need to be repeated if done within 3 days prior
- ECGs; see Table 7.
- Adverse events
- Concomitant medications

7.2.6 Cycles 2-4, Days 2, 3, 4, 5

- APR-246 (administered Days 1-4)
- Azacitidine (administered Days 1-5)
- Additional ECG monitoring in select patients; see Section 6.2
- Adverse events
- Concomitant medications

7.2.7 Cycles 2-4, Day 14

- CMP
- Adverse events
- Concomitant medications

7.2.8 Cycles 2-4, Day 28

- Physical exam with Weight
- Vital signs
- CBC
- CMP
- GVHD monitoring
- Adverse events
- Concomitant medications
- Disease assessment, blood every cycle, bone marrow end of Cycle/Month 3
- Chimerism, end of Cycle/Month 3

7.2.9 Cycles 5-12, Day 1 (Day 29 of prior cycle)

First dose of next cycle may be delayed up to 4 weeks.

- APR-246 (administered Days 1-4)
- Azacitidine (administered Days 1-5)
- Physical exam with Weight; Does not need to be repeated if done within 3 days prior
- Vital signs; Does not need to be repeated if done within 3 days prior
- CBC; Does not need to be repeated if done within 3 days prior

- CMP; Does not need to be repeated if done within 3 days prior
- Adverse events
- Concomitant medications

7.2.10 Cycles 5-12, Days 2, 3, 4, 5

- APR-246 (administered Days 1-4)
- Azacitidine (administered Days 1-5)
- Additional ECG monitoring in select patients; see Section 6.2
- Adverse events
- Concomitant medications

7.2.11 Cycles 5-12, Day 14

- CMP
- Adverse events
- Concomitant medications

7.2.12 Cycles 5-12, Day 28

Every cycle:

- Physical exam with Weight
- Vital signs
- CBC
- CMP
- GVHD evaluation
- Adverse events
- Concomitant medications
- Disease assessment, blood

Additionally, Every 3 cycles/months:

- Disease assessment, bone marrow end of Cycle/Month 6, 9, 12
    - Bone marrow aspirate sample and biopsy core are collected for MRD assessment and correlatives/exploratory (per Section 8.5) when bone marrow is sampled for disease assessment.
- Chimerism, end of Cycle/Month 6, 9, 12

Additionally, Every 6 cycles/months:

- Immune reconstitution, end of Cycle/Month 5, 11

7.3 End of Treatment Visit

Patients discontinuing study early should complete their end of treatment (EOT) visit within 30 days after their last dose. For patients who complete treatment per protocol, EOT is the last day of APR-246 and azacitidine dosing in Cycle 12.

If patients discontinue prior to receiving any APR-246 or azacitidine, the EOT is the date of relapse or Day 100 post-HSCT (the last day of post-transplant window eligibility requirement).

The following should be performed at EOT:

- Disease assessment (blood and bone marrow)
- Vital signs
- CBC
- CMP
- ECGs; see Table 7.
- Pregnancy test (women of child-bearing potential only)
- Adverse events
- Concomitant medications

7.4 30 Day Safety Follow-up Visit

This visit applies only to patients who received any APR-246 or azacitidine. This visit should occur 30 days after the last dose.

- Adverse events
- Concomitant medications

7.5 Long-Term Follow-up

This applies to all patients. Long term follow-up via phone call for survival will occur every 6 months until death or study closure. If GVHD or response assessment is conducted by the site per institutional standard of care, the site should report results to the sponsor until relapse is documented.

8.0 STUDY ASSESSMENTS

8.1 Safety Assessments

8.1.1 Safety Analysis

Safety data will be tabulated for all patients and include vital signs, laboratory parameters, ECGs and adverse events.

8.1.2 Safety Evaluation

A safety evaluation will be performed by the Safety Monitoring Committee after the first 6 patients have completed 1 cycle of APR-246 and azacitidine combination therapy. The Committee will decide if it is appropriate to continue at the current dose; or, in the event of the combination is not tolerated (e.g. patients experience dose limiting toxicity) the dose of APR-246 will be reduced for subsequent enrolled patients.

Adverse events and lab values will be reviewed. No formal analysis is planned.

8.1.3 Reporting of Adverse Events

8.1.3.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The AE reporting period starts from the day of signing consent. If an AE occurs before the first dose of study drug it will be considered a non-treatment emergent AE. All AEs will be collected for 30 days after the last dose of study drug; see Section 8.1.4 for GVHD reporting.

At each evaluation patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms.

All adverse events (except grade 1 and 2 laboratory abnormalities that do not require an intervention), regardless of causal relationship, are to be recorded in the case report form and source documentation. The Investigator must determine the intensity of any adverse events according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (see https://ctep.cancer.gov/protocoldevelopment/ electronic_applications/ctc.htm#ctc_50) and their causal relationship. Those AEs not covered by these criteria will be graded as follows:

1. Mild: Discomfort noticed, but no disruption of normal daily activity. Prescription drug not ordinarily needed for relief of symptom but may be given because of personality of patient.

2. Moderate: Discomfort sufficient to reduce or affect normal daily activity. Patient is able to continue in study; treatment for symptom may be needed.

3. Severe: Incapacitating, severe discomfort with inability to work or to perform normal daily activity. Severity may cause cessation of treatment with test drug; treatment for symptom may be given and/or patient hospitalized.

4. Life-Threatening: Symptom(s) place the patient at immediate risk of death from the reaction as it occurred; it does not include a reaction that, had it occurred in a more serious from, might have caused death.

5. Fatal: Event caused the death of the patient.

Adverse events will be followed until resolution or stabilization while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization, unless, in the Investigator's opinion the event is unlikely to resolve due to the patient's underlying disease, or until the patient starts a new treatment regimen or the patient is lost to follow-up.

8.1.3.2 Attribution Definitions

An adverse event is considered to be associated with the use of the Investigational agent if the attribution is determined as possible, probable or definite. Attribution of AEs will be recorded in the CRF as:

- Unrelated: The AE is clearly NOT related to the study treatment.
- Unlikely: The AE is doubtfully related to the study treatment.
- Possible: The AE may be related to the study treatment.
- Probable: The AE is likely related to the study treatment.
- Definite: The AE is clearly related to the study treatment.

8.1.3.3 Definition of an Unexpected Adverse Event

An unexpected adverse event is defined as any adverse drug experience, the specificity or severity of which is not consistent with the current Investigator Brochure; or, if an Investigator Brochure is not available, the specificity or severity of which is not consistent with the risk information described in this protocol or in the regulatory agency study authorization application.

Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the Investigator Brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

8.1.4 GVHD Adverse Event Reporting

All occurrences of GVHD will be reported as Adverse Events (or SAEs), regardless of their start date in relation to study drug. Acute GVHD will be followed until resolution, or until further improvement is no longer expected. Chronic GVHD events will be collected for 30 days after the last dose of study drug.

GVHD evaluation and grading will be performed per Harris 2016 (APPENDIX C) and Jagasia 2015 (APPENDIX D).[25,26]

8.1.4.1 Serious Adverse Event (SAE)

A serious adverse event is defined as any untoward medical occurrence that at any dose:

1. Results in death,

2. Is life-threatening (i.e., the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe),

3. Requires in-patient hospitalization or prolongation of existing hospitalization excluding that for pain management, disease staging/re-staging procedures, or catheter placement unless associated with other serious events,

4. Results in persistent or significant disability/incapacity, or

5. Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.1.4.2 Pregnancy

Any pregnancy diagnosed during the study, or that occurs within 30 days after stopping study medication, must be reported immediately to the Investigator. Pregnancy, in and of itself, is not regarded as an adverse event, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive medication. If the patient becomes pregnant while on-study, the study drug should be immediately discontinued. Pregnancy information about a female patient or a female partner of a male patient should be reported immediately from the time the Investigator first becomes aware of a pregnancy or its outcome. This will be performed by the Investigator completing a Pregnancy Form and emailing it or faxing it to the [redacted]

Any pregnancy complication, spontaneous abortion, elective termination of a pregnancy for medical reasons, outcome of stillbirth, congenital anomaly/birth defect, or serious adverse event in the mother will be recorded as an SAE and will be reported as described in Section 8.1.4.3.

8.1.4.3 Reporting of Serious Adverse Events

Adverse events classified as serious require expeditious handling and reporting to [redacted]o comply with regulatory requirements.

For any serious adverse event (SAE) that occurs from APR-246 consent up to 30 days after the last study drug administration, regardless of any opinion as to the relationship of the SAE to the study drug; or if any SAE that the Investigator feels is related to the study drug occurs later than 30 days after the last study drug administration, the [redacted]

All SAEs require that a Serious Adverse Event Report Form be completed and sent as a PDF via email (preferred method) or faxed to [redacted] at the address below within 24 hours of becoming aware of the event.

In the USA, SAEs will be reported to: [redacted]

8.1.4.4 Safety Monitoring Committee

The Safety Monitoring Committee, consisting of the Principal Investigator and Treating Investigator(s) (if different from the Principal Investigator), Sponsor and Medical Monitor, will perform a safety evaluation after the first 6 patients have completed 1 cycle of APR-246 and azacitidine combination therapy. Afterwards, safety will continue to be monitored and discussed during the regular study status meetings per the scheduled plan.

8.2 Efficacy Assessments

Treatment response will be assessed by review of BM/BMA and flow cytometry at the protocol-specified timepoints. In the LTFU period, assessments may be performed per institutional standard frequency.

CBC and differential will also be used to assess the presence of blasts in PB, as well as the extent of hematopoietic recovery.

Disease assessment, according to the Investigator, will be determined at each assessment according to the modified International Working Group (IWG) response criteria appropriate to the patient's underlying disease (Cheson 2003, 2006).[27, 28]

8.3 ECGs

For all patients, ECGs will be read at the timepoints listed in Table 7. Patients with screening or any pre-dose QTc of 450 ≤ QTc <470 ms should be subject to more intense ECG monitoring described in Section 6.2.

Table 7: ECG Timepoints

Schedule	# of ECGs	Timing
Pre screening	Triplicate	N/A
Post-transplant, pre-screening (before APR-246)	**Triplicate**	**N/A**
Cycle 1, Day 1	Single or replicate	Pre-dose; EOI/Post dose (4 hrs. after SOI; +/- 30 min.)
Cycle 2, Day 1		Pre-dose; EOI/Post dose (4 hrs. after SOI; +/- 30 min.)
Cycle 3, Day 1		Pre-dose; EOI/Post dose (4 hrs. after SOI; +/- 30 min.)
Cycle 4, Day 1		Pre-dose; EOI/Post dose (4 hrs. after SOI; +/- 30 min.)
EOT		N/A

EOT: end of treatment; SOI=start of infusion; EOI=end of infusion

8.4 Pharmacokinetics

PK blood samples will be collected per Table 8.

Table 8: PK Timepoints

Cycle	Study Day	Nominal time	Time-point
Cycle 1	Day 1	0 hours	0-2 hrs prior to APR-246 infusion
		0.75 hours	45 minutes after start of infusion
		4 hours	+/-5 min relative to the end of infusion
		5-6 hours	60-120 min AFTER end of infusion
	Day 2	24 hours	0-2 hrs prior to APR-246 infusion on Day 2

8.5 Correlatives/Exploratory Studies

Table 9: Biosampling Timepoints

Cycle	Timepoint(s)	Window	Blood and Bone Marrow for chimerism	Blood for immune reconstitution	BMA for MRD	BM biopsy for IHC
pre-transplant	Baseline	-28 to -1 prior to HSCT			X	X
post-transplant, before APR-246/ azacitidine	per institutional standard of care ◊	Day 1 to 100 post-transplant ◊	X	X		
APR-246/ azacitidine treatment period	Baseline ¥	-28 to -1 prior to starting APR-246 and azacitidine			X	X
APR-246/ azacitidine treatment period	end of C3, 6, 9, 12 (or EOT) ¥	up to 14 days	X		X	X
APR-246/ azacitidine treatment period	end of C5 and 11	+/- 3 days		X		

◊ A patient could proceed to APR-246/azacitidine treatment as early as Day 30 post-transplant. Therefore sampling frequency will depend on institutional practices and patient status.
¥ Bone marrow aspirate sample and biopsy core are collected when bone marrow is sampled for disease assessment.

8.5.1 Donor/Recipient Chimerism

Post-transplant donor/recipient chimerism will be monitored every 3 months by PCR on CD3/CD33 cells according to local practice. Refer to Table 9.

8.5.2 Immune System Reconstitution

Post-transplant immune system reconstitution will be monitored every 6 months by flow cytometry on blood samples according to local practice. Refer to Table 9.

8.5.3 MRD by NGS

Minimal/measurable residual disease (MRD) is monitored by a high-sensitivity NGS panel, including *TP53*, at a central laboratory. The *TP53* variant allele frequency (VAF) will be determined as a measure of MRD. Bone marrow aspirates will be obtained at pre-HSCT baseline, post-HSCT baseline, C3, C6, C9 and C12. Material for additional explorative biomarker research will be collected from the same samples. Refer to Table 9.

8.5.4 p53 IHC

p53 protein expression as marker for cells with *TP53* mutation will be monitored by immunohistochemistry (IHC) at a central laboratory. Bone marrow biopsy cores will be obtained at pre-HSCT baseline, post-HSCT baseline, C3, C6, C9 and C12. Refer to Table 9.

8.5.5 Post-Transplant Engraftment

Post-transplant donor engraftment via chimerism studies in blood and bone marrow will be summarized as continuous data for each dose level and overall respectively.

9.0 STATISTICS

Demographic and clinical variables for the study patients will be summarized using descriptive statistics (mean, standard deviation, median, inter-quartile range, range, frequency counts and percentages). Safety and efficacy data will be analyzed overall as well as separately for each dose cohort when appropriate.

9.1 Safety

Safety data including adverse events, vital signs, laboratory data, ECG, physical exam will be tabulated for the Safety Evaluable population which is all subjects who are registered on the study and received any dose of APR-246 or azacitidine. Adverse events will be tabulated by body system, preferred term, severity, and relationship to study drugs. The tabulation of laboratory parameters will include the normal ranges for each parameter. Each value will be classified as falling above, below, or within the normal range. Laboratory parameters will also be tabulated by maximum NCI-CTCAE v5 severity grade. Incidence and grade of acute and chronic GVHD at 1-year and cumulative will be summarized by number (%) of subjects for each dose level and overall.

9.2 Sample Size

The primary endpoint of the study is the relapse-free survival (RFS) at 12 months. The primary analysis will be done using the Kaplan-Meier method. Based upon the published data, the risk of relapse and non-relapse mortality in *TP53* mutated MDS is assumed to be ~40% and ~30% at 1 year, respectively. Thus the assumptions used for the sample size determination are:

- the null hypothesis: the RFS at 1 year is 30%,
- the alternative hypothesis: the RFS at 1 year is 50% or higher,
- accrual time: 24 months,
- follow-up time: 12 months,
- the RFS follows the exponential distribution.

With a one-sided significance level of 10%, 31 subjects will provide 90.1% power to test the null hypothesis against the alternative. The expected number of events during the study is 23 and the power was computed by a one-sided one-sample logrank test. The final analysis will be conducted when the follow-up time for all

censored patients exceed 12 months. The null hypothesis will be rejected if a one-sided p-value by the log-rank test is less than or equal to 0.1.

9.3 Efficacy Endpoint and Analyses

All efficacy analyses will be provided by using Efficacy Evaluable population. All subjects who are registered on the study and received at least one dose of APR-246 or azacitidine, and have at least one efficacy assessment, or had relapse/progression.

9.3.1 Relapse-Free Survival

The primary endpoint, RFS, is defined as the time from the date of registration to disease relapse after SCT, or death, whichever occurs earlier. If patients discontinued treatment due to toxicity, and withdrew consent without relapse disease (RD) or death at the time of data cut off, RFS will be censored at the date of the last assessment.

RFS will be analyzed using Kaplan-Meier methodology. Kaplan-Meier curves will be plotted. Median relapse-free survival will be estimated and their 95% confidence intervals based on Brookmeyer-Crowley methodology will be calculated.

9.3.2 Overall Survival

Overall survival (OS) is defined as the number of days from the date of registration to the date of death, irrespective of the cause. In the event of no death, overall survival will be censored at the last known alive date.

OS will be analyzed using the similar methods as RFS.

9.3.3 Non-Relapse Mortality

Non-relapse mortality (NRM) is defined as time to deaths without relapse/recurrence. Deaths from any cause without prior progression are events. Events related to the disease such as relapse and progression are competing events. Patients lost to follow-up are censored.

NRM will be analyzed using the similar methods as RFS.

9.3.4 Time to Progression (TTP)

Time to progression or relapse is time to first event related to the disease, such as disease progression, disease relapse/recurrence, death from disease progression, and/or initiation of any therapy given to prevent relapse. Deaths without prior relapse/recurrence (i.e., NRM) are competing events.

TTP will be analyzed using the similar methods as RFS.

9.3.5 Event-Free Survival (EFS)

EFS is defined as from registration to the first of: morphologic disease relapse, death from any cause, reappearance of a pre-transplant cytogenetic alteration, DLI for the purpose of treating MDS/AML, or institution of anti-MDS/AML therapy.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

10.1 Monitoring of the Study and Regulatory Compliance

The project manager, or designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the initiation site visit the case report forms (CRFs) will be reviewed. Other pertinent study materials will also be reviewed with the Investigator's research staff. During the course of the study, the monitor will make regular site visits in order to review protocol compliance, examine CRFs and individual subject's medical records and assure that the study is being conducted according to pertinent regulatory requirements. All CRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

10.2 Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current signed and dated curriculum vitae, a completed FDA Form 1572 and a financial disclosure statement to [redacted]. All Sub-investigators will be required to provide a current curriculum vitae and a financial disclosure statement to [redacted].

10.3 Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor or the Sponsor's representative ([redacted]). Any such changes which may affect a patient's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/IEC. The exception to this is where modifications are necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial (e.g., change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/IEC by the Principal Investigator.

10.4 Publication Policy

The Investigator agrees to inform the Sponsor of any publication or presentations on the study. All manuscripts, abstracts or presentations (in outline form with copies of

slides if available) will be submitted to the Sponsor and [redacted]x at least 30 days prior to the submission of the data for publication in order for the Sponsor to protect proprietary information. The Sponsor will review the submitted material within a reasonable period of time and will not unreasonably withhold publication permission.

11.0 ETHICAL CONSIDERATIONS

11.1 Informed Consent

The Investigator will obtain written informed consent from each patient, or their authorized representative, participating in the study. The form must be signed, witnessed and dated. The informed consent form will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013). Copies of the signed document should be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with the institution's Standard Operating Procedures.

In cases where minors or incapacitated subjects are to be included, two sets of information sheets might be needed according to national regulations. In addition to the information given to the patient's parent or legal representative, the patient should be given information according to his/her capacity to understand. This information should include, where appropriate, a statement that the patient's decision not to participate or to withdraw from a trial will be respected, even if consent is given by the parent/legal representative.

11.2 Institutional Review Board/Independent Ethics Committee

The study will not be initiated without approval of the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) and compliance with all administrative requirements of the governing body of the institution. This protocol, consent procedures, and any amendments must be approved by the IRB/IEC in compliance with current regulations of the FDA and the European Union as applicable and in accordance with ICH/GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IRB/IEC will be kept informed by the Investigator, [redacted] or the Sponsor, as required by national regulations, as to the progress of the study as well as to any serious and unexpected adverse events.

11.3 Patient Privacy

In order to maintain patient confidentiality, all case report forms, study reports and communications relating to the study will identify patients by initials and assigned

patient numbers; patients should not be identified by name. In accordance with local, national or federal regulations, the Investigator will allow the Sponsor or designee personnel access to all pertinent medical records in order to verify the data gathered on the case report forms and to audit the data collection process. Regulatory agencies such as the US Food and Drug Administration (FDA) and the UK Medicine and Healthcare Products Regulatory Agency (MHRA) may also request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the patient as outlined in the patient consent form.

12.0 DATA HANDLING AND RECORD KEEPING

12.1 Recording of Data

Data collected during the study will be entered in the patient's Case Report Form (CRF) by the investigational site staff. The staff will keep records of the patient's visit in the files considered as source documents for the site, e.g., hospital chart, research chart. The Investigator will be responsible for the recording of all data on the CRF and for submitting the data to the Sponsor or their designee in a timely manner. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the CRF.

The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data. To facilitate photocopying, entries must be recorded legibly in black ink only. Erroneous entries will be crossed out with a single line, so as to remain legible. The correct value will be entered above the error and then initialed and dated by the person authorized to make the correction.

12.2 Study Records

U.S. Federal laws require that an Investigator maintain all study records for the indication under investigation for two years following the date a Product Licensing Application is approved or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the FDA is notified.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

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APPENDIX A- KARNOFSKY PERFORMANCE SCALE

Condition	Performance status %	Comments
Able to carry on normal activity and to work. No special care needed.	100	Normal. No complaints. No evidence of disease.
	90	Able to carry on normal activity. Minor signs or symptoms of disease.
	80	Normal activity with effort. Some signs or symptoms of disease.
Unable to work. Able to live at home and care for most personal needs. A varying degree of assistance is needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled. Requires special care and assistance.
	30	Severely disabled. Hospital admission is indicated although death is not imminent.
	20	Hospitalization necessary. Very sick, active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

APPENDIX B- SCHEDULE OF EVENTS

Table 10: Pre-Screen, APR-246/azacitidine Screening, Cycles 1-4 (Treatment Period)

	Pre-screen	**HSCT**	**Post HSCT/ Screening Period APR-246/AZA (3)**	**APR-246/AZA Treatment Cycle 1**					**APR-246/AZA Treatment Cycles 2, 3, 4 (Cycles 5+; see Table 11)**				
Day	**-28 to -1 to HSCT**	**0**	**Max up to Day 100 post-HSCT**	**1 (first dose)**	**2, 3, 4**	**5**	**7, 14, 21**	**28**	**1 (D29 prior cycle)**	**2, 3, 4**	**5**	**14**	**28**
Window				**NMT 28 days after engraftment confirmation**			**+/- 3**	**+/-3 ***	**+28**			**+/-3**	**+/-3 ***
Informed Consent	X		X										
HSCT-eligibility	X												
TP53 mutation confirmation	X												
Engraftment confirmation			X (3)										
APR-246				X	X				X	X			
Azacitidine				X	X	X			X	X	X		
APR-246/AZA Eligibility			X (4)										
Karnofsky Performance Status			X										
Medical History and Transplant Details			X (4)										
Physical Exam with Weight			X (5)					X	X (5)				X
Vital Signs			X (5)				X	X	X (5)				X
CBC			X (5)				X	X	X (5)				X
CMP			X (5)				X	X	X (5)			X	X
Cardiac function (ECG)	X		X (5) (7)	X (7)	X (7)				X (7)	X (7)			
Pregnancy Test (1)	X		X (5)										
Disease Assessment (9)	X		X (4)					X (9)					X (9)
BM/BMA for Correlatives/ exploratory (2)	X (2)		X (2)										X (2)
GVHD monitoring			X					X					X
Blood sample (chimerism)													Cycle 3 (8)
Blood sample for flow (immune reconstitution)			X (4)										
PK sampling (blood)				X (6)	X (6)								

	Pre-screen	**HSCT**	**Post HSCT/ Screening Period APR-246/AZA (3)**	**APR-246/AZA Treatment Cycle 1**					**APR-246/AZA Treatment Cycles 2, 3, 4 (Cycles 5+; see Table 11)**				
Day	**-28 to -1 to HSCT**	**0**	**Max up to Day 100 post-HSCT**	**1 (first dose)**	**2, 3, 4**	**5**	**7, 14, 21**	**28**	**1 (D29 prior cycle)**	**2, 3, 4**	**5**	**14**	**28**
Window				**NMT 28 days after engraftment confirmation**			**+/- 3**	**+/-3 ***	**+28**			**+/-3**	**+/-3 ***
Adverse Events			X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X

(1) Pregnancy test applies to women of child-bearing potential only.
(2) Bone marrow aspirate sample and biopsy core are collected for correlatives/exploratory (per Section 8.5) when bone marrow is sampled for disease assessment.
(3) APR-246/azacitidine Screening Period starts when engraftment is confirmed between Day 30 to 100 post-HSCT. The first dose must be administered no more than 28 days after engraftment is confirmed.
(4) Perform within 28 days prior to first dose (Cycle 1 Day 1).
(5) Perform within 3 days prior to first dose (Cycle 1 Day 1); for Cycle 2+, do not need to repeat if done within 3 days prior to dosing.
(6) PK: see Section 8.4.
(7) Day 1 ECGs for all patients; see Table 7. Day 2, 3, 4 Additional ECG monitoring in select patients; see Section 6.2.
(8) CD3/CD33 in the blood should be done every 3 months same time marrows for disease assessment are being done. Additionally, whole bone marrow chimerism should be done from the marrow every 3 months collected at same time disease assessment labs are done
(9) Disease assessment by blood test must be done after every cycle. Response assessment based on CBC may utilize the most recently available bone marrow results. Disease assessment by bone marrow is done C3.
* Up to 14 day window is permitted for disease assessments.

Table 11: Cycle 5-12 (Treatment Period), EOT, 30 day Safety FUV, LTFU

	APR-246/AZA Treatment Cycles 5 - 12					EOT (5)	Follow-up safety visit	Long Term Follow-up (6)
Day	**1 (D29 prior cycle)**	**2, 3, 4**	**5**	**14**	**28**		**30 +/- 3 after last dose**	
Window	**+28**			**+/- 3**	**+/- 3 ***			
APR-246	X	X						
Azacitidine	X	X	X					
Physical Exam with Weight	X (3)				X			
Vital Signs	X (3)				X	X		
CBC	X (3)				X	X		
CMP	X (3)			X	X	X		
Cardiac function (ECG)	X (4)	X (4)				X		
Pregnancy Test (1)						X		
Disease Assessment					X (8)	X		X (6)
BM/BMA for Correlatives/exploratory (2)					C 6, 9, 12 (2)			
GVHD monitoring					X			X (6)
Blood sample (chimerism) (7)					C 6, 9, 12			
Blood sample for flow (immune reconstitution)					C 5, 11			
Adverse Events	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	
Survival								every 6 months

(1) Pregnancy test applies to women of child-bearing potential only.
(2) Bone marrow aspirate sample and biopsy core are collected for correlatives/exploratory (per Section 8.5) when bone marrow is sampled for disease assessment.
(3) Do not need to repeat if done within 3 days prior to dosing.
(4) After Cycle 4, perform additional ECG monitoring in select patients; see Section 6.2.
(5) EOT: see Section 7.3.
(6) LTFU applies to all patients. LTFU via phone call for survival will occur every 6 months until death or study closure. If GVHD or response assessment is conducted by the site per institutional standard of care, the site should report results to the sponsor until relapse is documented.
(7) CD3/CD33 in the blood should be done every 3 months same time marrows for disease assessment are being done. Additionally, whole bone marrow chimerism should be done from the marrow every 3 months collected at same time disease assessment labs are done
(8) Disease assessment by blood test must be done after every cycle. Response assessment based on CBC may utilize the most recently

available bone marrow results. Disease assessment by bone marrow is done C3.
***** Up to 14 day window is permitted for disease assessments**.**

APPENDIX C- ACUTE GVHD GRADING SCALE

GVHD Target Organ Staging

Stage	Skin (Active Erythema Only)	Liver (bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	< 2 mg/dl	No intermittent nausea, vomiting, or anorexia	<500 mL/day or <3 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dl	Persistent nausea, vomiting or anorexia	500-999 mL/day or 3-4 episodes/day
2	Maculopapular rash 25%-50% BSA	3.1-6 mg/dl		1000-1500 mL/day or 5-7 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dl		>1500 mL/day or >7 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dl		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

Overall clinical grade (based on most severe target organ involvement):

Grade 0:	No Stage 1-4 of any organ.
Grade 1:	Stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade 2:	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
Grade 3:	Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI.
Grade 4:	Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.

Reference: Harris AC, et al. Biol Blood Marrow Transplant 2016; 22:4

APPENDIX D- CHRONIC GVHD GRADING SCALE

Excerpted from Jagasia 2015: The following outlines the computation of the chronic GVHD global severity scoring, which is categorized as mild, moderate, or severe.

NIH Global Severity of chronic GVHD

Mild chronic GVHD:
1 or 2 organs involved with no more than score 1 *plus*
Lung score 0

Moderate chronic GVHD:
3 or more organs involved with no more than score 1
OR,
At least 1 organ (not lung) with a score of 2
OR,
Lung score 1

Severe chronic GVHD:
At least 1 organ with a score of 3
OR
Lung score of 2 or 3

KEY POINTS:
In skin: higher of the 2 scores to be used for calculating global severity.
In lung: FEV1 is used instead of clinical score for calculating global severity.
If the entire abnormality in an organ in noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the second organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).